

AMENDMENTS TO THE CLAIMS

1. (Original) A pharmaceutical drug and/or veterinary drug comprising an effective amount of one or more members selected from the group consisting of an IP-10 protein, and IP-10 analogues and IP-10 derivatives having at least a deletion, addition, and/or substitution of one or more amino acid residues in IP-10 and having a biological activity essentially equal or equivalent to that of intact IP-10,

the pharmaceutical drug and/or veterinary drug being an agent selected from the group consisting of (a) an agent for activating conceptus migration, (b) an agent for promoting conceptus implantation on the uterine wall, (c) an agent for treating sterility, (d) an agent for promoting pregnancy, (e) an agent for controlling interaction between conceptus and maternal system, (f) an agent for activating immunocyte migration, and (g) an agent for controlling immune function in the uterus.

2. (Original) The pharmaceutical drug and/or veterinary drug according to claim 1, wherein the IP-10 is derived from mammal including human, bovine, buffalo, equine, donkey, ovine, goat, camel, swine, deer, reindeer, yak, canine, cat, and ape.

3. (Original) A method for obtaining a biological activity selected from the group consisting of (a) activation of conceptus migration, (b) promotion of conceptus implantation on the uterine wall, (c) treatment of sterility, (d) promotion of pregnancy, (e) control of interaction between conceptus and maternal system, (f) activation of immunocyte migration, and (g) control of immune function in the uterus,

which comprises treating a sample with a material selected from the group consisting of IP-10, and IP-10 analogues and IP-10 derivatives having at least a deletion, addition, and/or substitution of one or more amino acid residues in IP-10 and having a biological activity essentially equal or equivalent to that of intact IP-10.

4. (Original) A reagent comprising a material selected from the group consisting of IP-10, and IP-10 analogues and IP-10 derivatives having at least a deletion, addition, and/or substitution of one or more amino acid residues in IP-10 and having a biological activity

essentially equal or equivalent to that of intact IP-10 and being useful for the method according to claim 3.

5. (Original) An assay for measuring an IP-10 activity to determine a biological activity selected from the group consisting of (a) activation of conceptus migration, (b) promotion of conceptus implantation on the uterine wall, (c) treatment of sterility, (d) promotion of pregnancy, (e) control of interaction between conceptus and maternal system, (f) activation of immunocyte migration, and (g) control of immune function in the uterus.

6. (Original) A reagent that is useful for the assay according to claim 5.

7. (Original) A pharmaceutical drug and/or veterinary drug comprising a nucleic acid having a nucleotide sequence encoding a member selected from the group consisting of IP-10, and IP-10 analogues and IP-10 derivatives having at least a deletion, addition, and/or substitution of one or more amino acid residues in IP-10 and having a biological activity essentially equal or equivalent to that of intact IP-10,

the pharmaceutical drug and/or veterinary drug being an agent selected from the group consisting of (a) an agent for activating conceptus migration, (b) an agent for promoting conceptus implantation on the uterine wall, (c) an agent for treating sterility, (d) an agent for promoting pregnancy, (e) an agent for controlling interaction between conceptus and maternal system, (f) an agent for activating immunocyte migration, and (g) an agent for controlling immune function in the uterus.

8. (Original) A pharmaceutical drug and/or veterinary drug comprising a nucleic acid selected from the group consisting of

- (i) a nucleotide sequence comprising at least one open reading frame portion present in SEQ ID NO: 1 and,
- (ii) a nucleotide sequence capable of hybridizing with at least one sequence described in the above (i) under a stringent condition, and
- (iii) a nucleotide sequence encoding a peptide containing an amino acid sequence at least

80% homologous to a polypeptide shown in FIG. 2 or shown by SEQ ID NO: 2, wherein said peptide has a biological activity substantially equal to that of IP-10 (for example, ovine IP-10), including a biological activity, or an antigenic equivalent thereof, selected from the group consisting of (a) activation of conceptus migration, (b) promotion of conceptus implantation on the uterine wall, (c) treatment of sterility, (d) promotion of pregnancy, (e) control of interaction between conceptus and maternal system, (f) activation of immunocyte migration, and (g) control of immune function in the uterus,

the pharmaceutical drug and/or veterinary drug being an agent selected from the group consisting of (a) an agent for activating conceptus migration, (b) an agent for promoting conceptus implantation on the uterine wall, (c) an agent for treating sterility, (d) an agent for promoting pregnancy, (e) an agent for controlling interaction between conceptus and maternal system, (f) an agent for activating immunocyte migration, and (g) an agent for controlling immune function in the uterus.

9. (Original) A pharmaceutical drug comprising a compound, or a salt thereof, for promoting or inhibiting a biological activity selected from the group consisting of (a) activation of conceptus migration, (b) promotion of conceptus implantation on the uterine wall, (c) treatment of sterility, (d) promotion of pregnancy, (e) control of interaction between conceptus and maternal system, (f) activation of immunocyte migration, and (g) control of immune function in the uterus,

said biological activity being owned by

(A) a material, or its salt, selected from the group consisting of IP-10 and IP-10 analogues or IP-10 derivatives having at least a deletion, addition, and/or substitution of one or more amino acid residues in IP-10 and having biological activities essentially equal or equivalent to those of intact IP-10, or

(B) a nucleic acid selected from the group consisting of

(i) a nucleotide sequence comprising at least an open reading frame portion present in SEQ ID NO: 1 and,

(ii) a nucleotide sequence capable of hybridizing with at least one sequence described in the above (i) under a stringent condition, and

(iii) a nucleotide sequence encoding a peptide containing an amino acid

sequence at least 80% homologous to a polypeptide in Fig. 2 or shown by SEQ ID NO: 2, wherein said peptide has a biological activity substantially equal to that of IP-10 (for example, ovine IP-10), including a biological activity, or an antigenic equivalent thereof, selected from (a) activating conceptus migration, (b) promoting conceptus implantation on the uterine wall, (c) treating sterility, (d) promoting pregnancy, (e) controlling interaction between conceptus and maternal system, (f) activating immunocyte migration, and (g) controlling immune function in the uterus.

10. (Original) A method or kit for screening a compound promoting or inhibiting a biological activity owned by a member selected from the group consisting of IP-10, IP-10 analogues and IP-10 derivatives having at least a deletion, addition, and/or substitution of one or more amino acid residues in IP-10 and having a biological activity essentially equal or equivalent to that of intact IP-10, or salts thereof, and IP-10 nucleic acids encoding the same, wherein the biological activity is selected from the group consisting of (a) activation of conceptus migration, (b) promotion of conceptus implantation on the uterine wall, (c) treatment of sterility, (d) promotion of pregnancy, (e) control of interaction between conceptus and maternal system, (f) activation of immunocyte migration, and (g) control of immune function in the uterus,

the method or the kit using or comprising (A) a compound, or its salt, selected from the group consisting of IP-10, the IP-10 analogues and the IP-10 derivatives, or (B) a material selected from the group consisting of nucleic acids encoding the compound in (A), vectors containing the nucleic acid, and host cells transformed with the nucleic acid or the vector.

11. (Original) The method or kit according to claim 10, wherein the method or kit is useful for screening a compound promoting the production of IP-10 and preventing development and/or progress of sterility.

12. (Currently amended) A compound for controlling the production of IP-10, which is obtained or identified by screening with the method or kit according to claim 10 or 11.

13. (Original) A reagent for detecting the presence of a mutated portion capable of altering the activity or expression of IP-10 wherein said mutated portion is present in IP-10, a gene encoding IP-10, or the corresponding RNA, and genetically diagnosing a disease associated with IP-10.

14. (Original) The diagnostic reagent according to claim 13, which comprises at least a material selected from the group consisting of a restriction enzyme capable of specifically recognizing a mutation in IP-10 gene, mRNA, or hnRNA, and an isoschizomer thereof; and an oligonucleotide primer useful in amplification of a gene including a mutation in IP-10 gene, mRNA, or hnRNA.

15. (Original) A method for genetic diagnosis of a disease associated with an IP-10 gene which comprises the steps of;

(a) preparing a nucleic acid sample,
(b) subjecting the nucleic acid sample in the step (a) to gene amplification to give amplified nucleic acid fragments containing one or more mutations in the IP-10 gene, and
(c) determining the presence of mutation in the nucleic acid fragment prepared in the step (c).

16. (Original) A method for determining or diagnosing a biological activity in a specimen which comprises quantitating an IP-10 polynucleotide present in the specimen and using as an indicator the IP-10 polynucleotide amount to determine or diagnose a biological activity level in the specimen

wherein said biological activity is selected from the group consisting of:

(a) activation of conceptus migration, (b) promotion of conceptus implantation on the uterine wall, (c) treatment of sterility, (d) promotion of pregnancy, (e) control of interaction between conceptus and maternal system, (f) activation of immunocyte migration, and (g) control of immune function in the uterus.

17. (Original) A method for determining or diagnosing a biological activity in a specimen which comprises quantitating an IP-10 protein present in the specimen and

using as an indicator the IP-10 protein amount to determine or diagnose a biological activity level in the specimen

wherein said biological activity is selected from the group consisting of:
(a) activation of conceptus migration, (b) promotion of conceptus implantation on the uterine wall, (c) treatment of sterility, (d) promotion of pregnancy, (e) control of interaction between conceptus and maternal system, (f) activation of immunocyte migration, and (g) control of immune function in the uterus.

18. (Original) A composition for determining or diagnosing a biological activity in a specimen which comprises at least a member selected from an oligonucleotide or polynucleotide which hybridizes with IP-10 polynucleotide under a stringent condition,

wherein the biological activity is selected from the group consisting of:
(a) activation of conceptus migration, (b) promotion of conceptus implantation on the uterine wall, (c) treatment of sterility, (d) promotion of pregnancy, (e) control of interaction between conceptus and maternal system, (f) activation of immunocyte migration, and (g) control of immune function in the uterus.

19. (Original) A nucleic acid array for determining or diagnosing a biological activity level in a specimen which comprises (i) an oligonucleotide or polynucleotide which hybridizes with IP-10 polynucleotide under a stringent condition or (ii) IP-10 polynucleotide,

wherein the biological activity is selected from the group consisting of:
(a) activation of conceptus migration, (b) promotion of conceptus implantation on the uterine wall, (c) treatment of sterility, (d) promotion of pregnancy, (e) control of interaction between conceptus and maternal system, (f) activation of immunocyte migration, and (g) control of immune function in the uterus.

20. (Original) A primer set used for PCR-amplification of IP-10 polynucleotide in a specimen and determining or diagnosing the degree of a biological activity of a specimen,

wherein the biological activity is selected from the group consisting of:
(a) activation of conceptus migration, (b) promotion of conceptus implantation on the

uterine wall, (c) treatment of sterility, (d) promotion of pregnancy, (e) control of interaction between conceptus and maternal system, (f) activation of immunocyte migration, and (g) control of immune function in the uterus.

21. (Original) A diagnosis kit for determining or diagnosing the degree of a biological activity of a specimen comprising at least one antibody capable of recognizing IP-10,

wherein the biological activity is selected from the group consisting of:

(a) activation of conceptus migration, (b) promotion of conceptus implantation on the uterine wall, (c) treatment of sterility, (d) promotion of pregnancy, (e) control of interaction between conceptus and maternal system, (f) activation of immunocyte migration, and (g) control of immune function in the uterus.

22. (Original) A diagnosis kit for determining or diagnosing the degree of a biological activity of a specimen comprising at least elements consisting of

(i) an immobilized antibody capable of recognizing IP-10, and
(ii) an antibody capable of recognizing an IP-10 epitope other than that being recognized by the antibody (i),

wherein the biological activity is selected from the group consisting of:

(a) activation of conceptus migration, (b) promotion of conceptus implantation on the uterine wall, (c) treatment of sterility, (d) promotion of pregnancy, (e) control of interaction between conceptus and maternal system, (f) activation of immunocyte migration, and (g) control of immune function in the uterus.

23. (Original) A method for measuring the degree of abnormality or its risk associated with a biological activity selected from the group consisting of:

(a) activation of conceptus migration, (b) promotion of conceptus implantation on the uterine wall, (c) treatment of sterility, (d) promotion of pregnancy, (e) control of interaction between conceptus and maternal system, (f) activation of immunocyte migration, and (g) control of immune function in the uterus,

the method comprising at least the steps of:

(i) contacting a biological specimen with a support immobilized with an antibody capable

of recognizing IP-10;

- (ii) washing the support contacted with the biological specimen;
- (iii) contacting the support contacted with the biological specimen with a labeled antibody, wherein the labeled antibody is capable of recognizing an epitope on IP-10 other than that being recognized by the immobilized antibody;
- (iv) measuring a label on the support or a free label;
- (v) using the amount of the label measured in the step (iv) as an indicator of the amount of IP-10 and comparing it with a result of a normal biological specimen; and
- (vi) using the amount of IP-10 being significantly different from the result of the normal biological specimen as an indicator of the degree of abnormality or its risk associated with the biological activity.

24. (Original) A method for measuring the degree of abnormality or its risk associated with a biological activity selected from the group consisting of:

- (a) activation of conceptus migration, (b) promotion of conceptus implantation on the uterine wall, (c) treatment of sterility, (d) promotion of pregnancy, (e) control of interaction between conceptus and maternal system, (f) activation of immunocyte migration, and (g) control of immune function in the uterus,

the method comprising at least the steps of:

- (i) preparing RNA from a biological specimen;
- (ii) separating the RNA prepared in the step (i) by electrophoresis;
- (iii) hybridizing the RNA separated in the step (ii) with a labeled nucleotide probe which hybridizes IP-10 polynucleotide under a stringent condition;
- (iv) using the amount of the label hybridized in the step (iii) as an indicator of expression of IP-10 polynucleotide and comparing it with a result of a normal biological specimen; and
- (v) using the amount of expression of IP-10 polynucleotide being significantly different from the result of the normal biological specimen as an indicator of the degree of abnormality or its risk associated with the biological activity.

25. (Original) A method for measuring the degree of abnormality or its risk associated

with a biological activity selected from the group consisting of:

(a) activation of conceptus migration, (b) promotion of conceptus implantation on the uterine wall, (c) treatment of sterility, (d) promotion of pregnancy, (e) control of interaction between conceptus and maternal system, (f) activation of immunocyte migration, and (g) control of immune function in the uterus,

the method comprising at least the steps of:

- (i) preparing RNA from a biological specimen;
- (ii) generating a first cDNA strand by using the RNA prepared in the step (i) as a template with a dT primer;
- (iii) amplifying IP-10 polynucleotide by PCR using the cDNA generated in the step (ii) as a template with a primer set for amplifying the IP-10 polynucleotide;
- (iv) separating the PCR product in the step (iii) by electrophoresis;
- (v) hybridizing the PCR product separated in the step (iv) with a labeled nucleotide probe which hybridizes IP-10 polynucleotide under a stringent condition;
- (vi) using the amount of the label hybridized in the step (v) as an indicator of expression of IP-10 polynucleotide and comparing it with a result of a normal biological specimen; and
- (vii) using the amount of expression of IP-10 polynucleotide being significantly different from the result of the normal biological specimen as an indicator of the degree of abnormality or its risk associated with the biological activity.

26. (Original) A method for measuring the degree of abnormality or its risk associated with a biological activity selected from the group consisting of:

(a) activation of conceptus migration, (b) promotion of conceptus implantation on the uterine wall, (c) treatment of sterility, (d) promotion of pregnancy, (e) control of interaction between conceptus and maternal system, (f) activation of immunocyte migration, and (g) control of immune function in the uterus,

the method comprising at least the steps of:

- (i) treating a biological specimen for tissue fixation;
- (ii) sectioning the fixed tissue prepared in the step (i);
- (iii) staining the sectioned tissue immunohistologically with an antibody capable of

recognizing IP-10;

- (iv) comparing the degree of the immunohistological stained biological specimen with that of a normal biological specimen; and
- (v) using the amount of IP-10 protein being significantly different from the result of the normal biological specimen as an indicator of the degree of abnormality or its risk associated with the biological activity.

27. (Original) A method for measuring the degree of abnormality or its risk associated with a biological activity selected from the group consisting of:

- (a) activation of conceptus migration, (b) promotion of conceptus implantation on the uterine wall, (c) treatment of sterility, (d) promotion of pregnancy, (e) control of interaction between conceptus and maternal system, (f) activation of immunocyte migration, and (g) control of immune function in the uterus,

the method comprising at least one step selected from the group consisting of:

- (i) amplifying IP-10 polynucleotide in the biological specimen by PCR using a primer set for amplifying the IP-10 polynucleotide;
- (ii) analyzing a nucleic acid fraction separated from the biological specimen by using (I) an oligonucleotide or polynucleotide which hybridizes with IP-10 polynucleotide under a stringent condition or (II) a nucleic acid array having IP-10 polynucleotide; and
- (iii) hybridizing a nucleic acid fraction separated from the biological specimen with an oligonucleotide or polynucleotide which hybridizes with IP-10 polynucleotide under a stringent condition; and

the step of measuring the amount of IP-10 polynucleotide in the biological specimen and then comparing the amount of the IP-10 polynucleotide in the specimen with that in a normal biological specimen.

28. (Currently amended) The method according to ~~any one of claims 23 to 27~~ claim 23 for measuring abnormality or its risk associated with a biological activity selected from the group consisting of:

- (a) activation of conceptus migration, (b) promotion of conceptus implantation on the uterine wall, (c) treatment of sterility, (d) promotion of pregnancy, (e) control of

interaction between conceptus and maternal system, (f) activation of immunocyte migration, and (g) control of immune function in the uterus,
by quantitatively measuring IP-10 protein or expression of IP-10 polynucleotide.

29. (Currently amended) A reagent used in the method according to ~~any one of claims 23 to 27~~ claim 23 for measuring abnormality or its risk associated with a biological activity selected from the group consisting of:

(a) activation of conceptus migration, (b) promotion of conceptus implantation on the uterine wall, (c) treatment of sterility, (d) promotion of pregnancy, (e) control of interaction between conceptus and maternal system, (f) activation of immunocyte migration, and (g) control of immune function in the uterus,

wherein the reagent contains an antibody selected from the group consisting of (i) an antibody capable of recognizing IP-10, (ii) an antibody capable of binding an epitope on IP-10 which is different from that recognized by the antibody (i), (iii) an immobilized antibody (i) or antibody (ii), and (iv) a labeled antibody (i) or antibody (ii).

30. (Original) A method for measuring or diagnosing the degree of abnormality or its risk associated with a biological activity selected from the group consisting of:

(a) activation of conceptus migration, (b) promotion of conceptus implantation on the uterine wall, (c) treatment of sterility, (d) promotion of pregnancy, (e) control of interaction between conceptus and maternal system, (f) activation of immunocyte migration, and (g) control of immune function in the uterus,

by measuring an amount of IP-10 protein or expression of IP-10 polynucleotide in a sample by using an antibody capable of recognizing IP-10.

31. (Original) A reagent for measuring or diagnosing the degree of abnormality or its risk associated with a biological activity selected from the group consisting of:

(a) activation of conceptus migration, (b) promotion of conceptus implantation on the uterine wall, (c) treatment of sterility, (d) promotion of pregnancy, (e) control of interaction between conceptus and maternal system, (f) activation of immunocyte migration, and (g) control of immune function in the uterus,

the reagent containing an antibody capable of recognizing IP-10 for measuring an amount of IP-10 protein or expression of IP-10 polynucleotide in a sample.